Prostate cancer

Demographics

Commonest male cancer in UK: Approximately 30,000 new cases per yr
Second leading cause of death in men: 10,000 deaths per yr
Incidence increasing – presumed secondary to increased use of PSA
Mortality falling – ? due to improved treatment/screening
Predominantly a disease of older men – thus large geographical differences based on life-expectancy; 15% prevalence in developed vs. 4% prevalence in developing countries
Incidence of undetected foci of latent CaP at post-mortem similar (12%) around world (Hong Kong, Singapore, Sweden, Germany, Jamaica, Israel; Breslow 1977), yet wide geographical differences in rates of clinical disease. Moreover, Japanese migrants have higher rates of PCa cf. first-degree relatives living in Japan (Shimuzu 1991) implicating environmental factors in modifying progression from latent to clinically significant disease.
Lifetime risk of CaP 16.7% (1 in 6), yet risk of CaP death 0.03% (1 in 30) (Jemal 2002) – challenge for modern urologists to distinguish between indolent and aggressive forms of the disease.

Aetiology

Age

- Very uncommon in men < 50 yrs – accounts for less than 0.1% of all cases
- 75% of cases in men > 65 yrs
- 80% of men $\geqslant$ 80 yrs harbour foci of prostate cancer (Breslow 1977)

Heredity

One first-degree relative	RR increased x2
Two first-degree relatives	RR increased x4
Hereditary CaP*	RR increased x5 (Bratt 2002)

*Hereditary CaP defined as 3 or more relatives, 3 successive generations, or 2 individuals < 55yrs (Carter 2002). Familial CaP defined as one or more affected relatives
Thought to account for up to 10% of prostate cancer cases
Responsible genes: HPC (1q24-25)/RNaseL; BRCA2 etc. HPC thought to code for RNaseL, a protein which shepherds virally infected cells towards apoptosis. Mutations in HPC gene lead to defective RNaseL and failed clearance of virus, presumed to lead to DNA mutation and carcinogenesis.

Diet

- Dietary fat
  - CaP higher in countries with high dietary fat intake
  - Animal models show PCa growth proportional to dietary fat intake (Clinton 1988) High fat induces oxidative stress
  - However high fat diets a/w low antioxidants – may be confounding
- Antioxidants
  - Lycopenes, green tea (active constituemt epigallocatechin-3-

gallate (EGCG)), and isoflavanoids (active constituent genistein) associated with reduced risk of prostate cancer.

Exogenous oestrogen exposure

Some evidence to support genetic 'imprinting' following foetal exposure to oestrogenic compounds (ie bisphenol a; Timms 2005)

Chronic prostate infection

Accumulating evidence supporting a role for chronic inflammation in genesis of prostate cancer

Hx STI or prostatitis - RR increased 1.5x

CaP associated with increased AB vs. viruses and increased cytokines

CMV, poliovirus and HPV found in CaP

Inflammation and proliferative inflammatory atrophy a/w and may be precursors of Ca (deMarzo 2004)

Multiple defects in genes a/w protection against infection/oxidative stress/inflammation (HPC1, MSR etc.)

Impaired ability to combat oxidative stress explains interest in chemoprotective effect of anti-oxidants (see below)

Ejaculation

Frequent ejaculation persistently reported to be protective for prostate cancer (RR ~ 0.75) for ejaculation ≥ 21/month (Leitzman 2004).

Mechanism unknown

Vasectomy

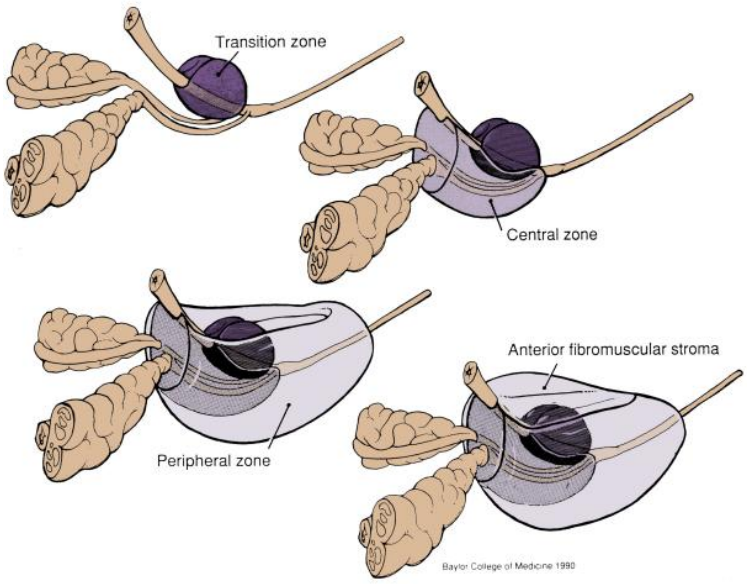
Increased RR = 1.4 which increases by 10% q.10 yrs after vasectomy (Dennis 2002). Mechanism unknown

Smoking

No definite evidence for smoking

Pathology

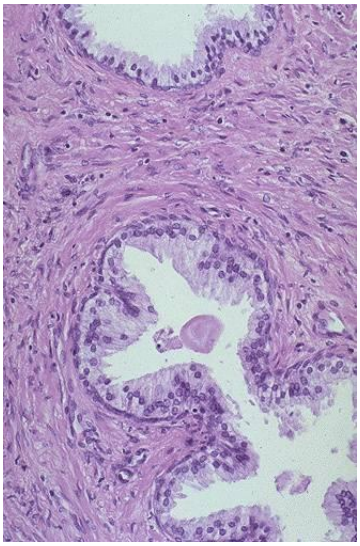
Macroscopic



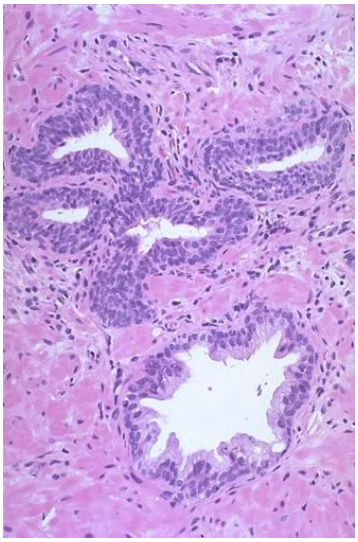
Peripheral zone	70% glands	70% cancers	
Transitional zone	5% glands	25% cancers	
Central zone	25% glands	5% cancers	(McNeal 1988)

Prostate lacks a discrete histological capsule – therefore ‘extraprostatic extension’ not ‘capsular penetration’

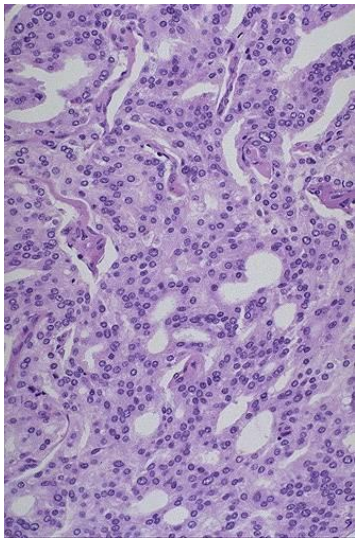
Microscopic



Normal



PIN



Adenocarcinoma

Prostate intraepithelial neoplasia (PIN)

Architecturally benign glands lined by cytologically atypical cells
Low grade vs. high grade based on nucleoli prominence
Low grade difficult to discern from benign and not associated with increased risk of cancer on subsequent Bx – not commented on
High grade a/w prostate Ca
↑ HGPIN in prostates with Ca cf. those without
More HGPIN = more multifocal ca
Similar molecular changes
Co-localisation to PZ
HGPIN not a/w PSA elevation
Overall risk of HGPIN 5% on initial biopsy
Risk of cancer on subsequent biopsy 26% - not significantly different from benign in 6/8 clinical studies (Epstein 2006) – therefore no indication for repeat biopsy
High volume (> 4 cores) HGPIN is associated with 39% risk of Ca (Netto & Epstein 2006). Re-biopsy recommended

Atypical findings

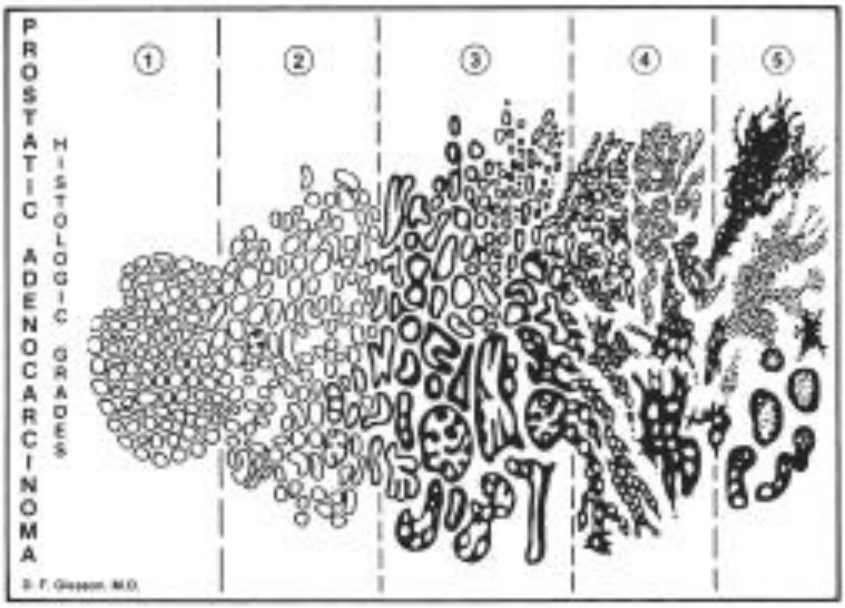
Best described as findings suggestive but not amounting to Ca
Variously reported as ‘atypical hyperplasia’ or ‘atypical small acinar proliferation’ – move to describe them simply as ‘atypical glands’
Approximate incidence ~5% of biopsies
Associated with likelihood of cancer on subsequent biopsy of ~40%
Expert opinion worthwhile – reclassified as cancer in 40% of cases in one study (Chan 2000)
NB. Atypical adenomatous hyperplasia is a benign finding a/w BPH found in ~1% specimens, often after TUR. Not a/w cancer

Prostate adenocarcinoma

Glands or acini lined by two layers of cells: outer secretory layer of columnar cells and inner layer of more rounded basal cells sitting on basement membrane. Glands separated by fibromuscular stroma

Diagnosis of invasive adenocarcinoma = combination of cytological atypia and architectural changes

Gleason grading system purely architectural however – relates to degree of glandular differentiation, which independently prognostic (Gleason 1974).
NB. Primary *and* secondary patterns found to be individually prognostic – therefore combined to form Gleason grade



Grade 1	Small uniform glands
Grade 2	More stroma between small/medium sized glands
Grade 3	Infiltrative, more heterogenous size
Grade 4	Large irregular cribiform glands
Grade 5	No glandular differentiation; sheets/cords/single cells

Gleason grading tutorial at www.pathology.jhu.edu/prostate
Gleason 4+3 has worse prognosis than 3+4 (Chan 2000)
Diagnostic difficulty?

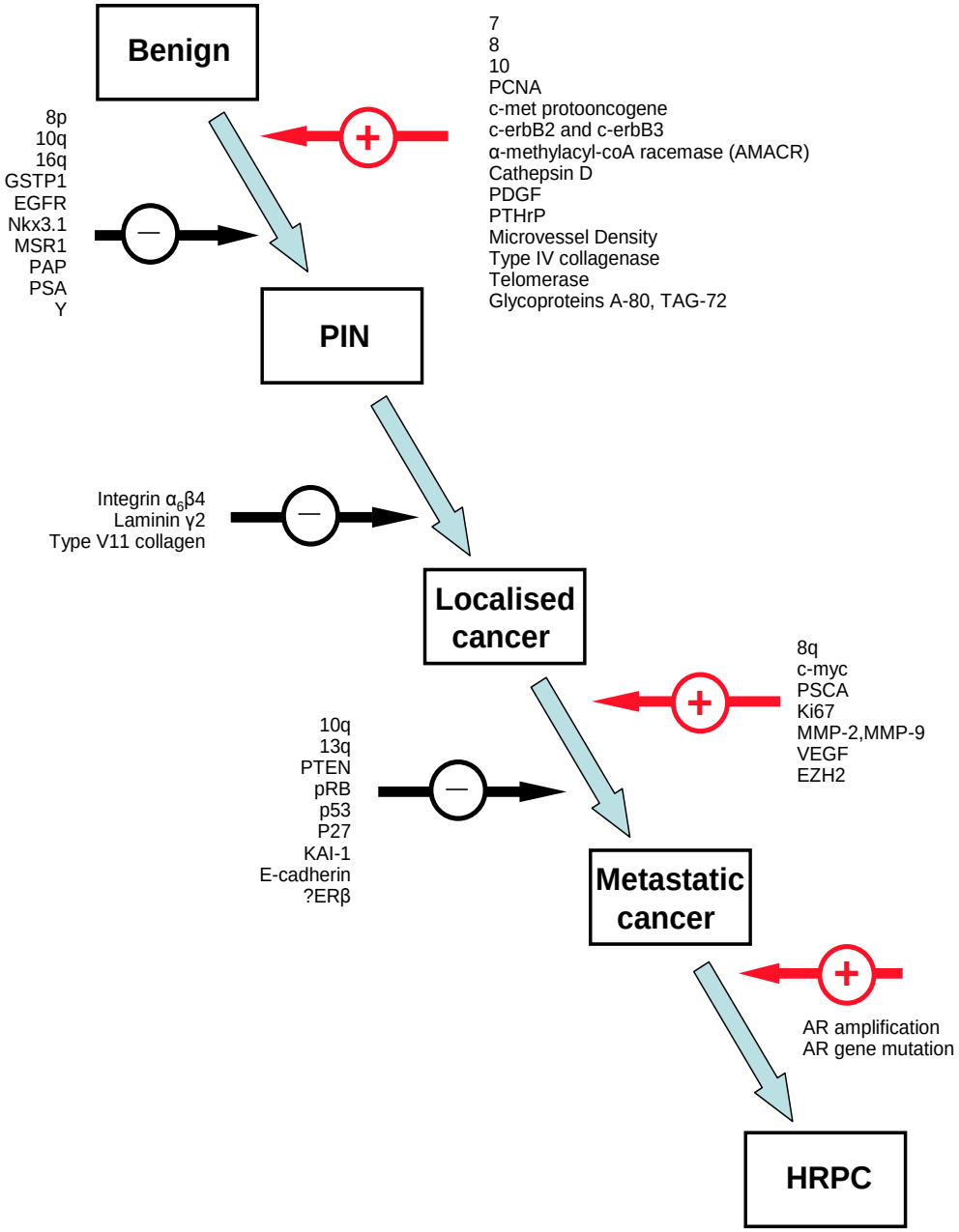
- Benign glands positive for HMK cytokeratin and p63, whereas PCa negative
- Benign glands have high PSA, low human kallikrein 2 expression: malignant glands have low PSA, high hK2 expression
- Alpha methylacyl-CoA racemase (AMACR) positive in CaP and PIN but FN (18%) rate reported (Epstein 2004)

Other prostate cancer subtypes

Intraductal carcinoma: 0.5% CaP. Arise from prostate ducts. Typically advanced and aggressive (Gleason 8 typically).
Mucinous adenocarcinoma: rare, aggressive form. a/w early mets, ↑ ALP & PSA

Small cell carcinoma: identical to lung; majority non-secreting, occasionally ACTH or ADH. Average survival < 12 months
Leiomyosarcoma most common mesenchymal tumour of prostate but extremely rare.

Molecular



Major events
Loss of GTSP1: early; seen in 90% CaP; lost exclusively by hypermethylation; codes for glutathione-s-transferase pi, which protects against free radicals
Deletion of 8p: early; 50-80% of Cap; ? leads to loss of macrophage scavenging receptor 1 (MSR1), limiting response to infection
Gain of 8q: late; 90% of HRPC; candidate gene c-myc (?Pr.stem cell Ag)
Loss of 10q: late; loss of PTEN, negative regulator of oncogene Akt

Diagnosis

DRE
Operator dependent
Poor reproducibility
Relatively low sensitivity approximating 50%; specificity of 80%
Used in concert with PSA to improve PPV
Schroder (from ERSPC 1998)
PPV 4-11% in patients with PSA < 3
PPV 33-80% in patients with PSA <10
17% of cancers (n=473) would have been missed by PSA alone
Standard DRE does not influence PSA levels within SE of assay

PSA
33 kD glycoprotein & serine protease (enzyme)
Member of human kallikrein family (hKLK3) closely related to hKLK2
Product of KLK3 gene located on chromosome 19
Acts on gel-forming proteins semenogelin and fibronectin to liquify sperm
Released from prostate luminal epithelial cells - 10^6 fold more concentrated in semen cf. serum.
Released as pro-PSA with a 7 amino-acid leader which is cleaved by hKLK2 to produce active PSA. Inactivated by proteolytic processing
Circulates bound to antiproteases alpha-1 anti-chymotrypsin (ACT), alpha-2 macroglobulin (A2M) and alpha-1 antiprotease (API)
PSA-ACT ~60-90%. Small proportion (5-40%) circulates as free inactive PSA
Assays currently measure free PSA, total PSA, PSA-ACT, and pro-PSA.
Cannot currently measure other complexes
Half-life 2-3 days (60 hours according to Campbell's): complex PSA cleared by liver; free PSA cleared by kidney
PSA organ specific, not cancer specific – 1g of BPH produces 0.15-0.3ng/ml
Cancer cells produce less PSA (mRNA and protein) than normal and BPH cells. Reason for elevation in cancer (and inflammation) due to disruption of architecture of glandular prostate.
PSA produced from cancer cells avoids proteolytic processing. Thus proportion of PSA circulating in inactivated free form reduced.

Clinical uses of PSA-testing

Single cutpoints

Table 2: PSA value and risk of CaP

PSA ng/mL	PPV for cancer
0-1	2.8-5%
1-2.5	10.5-14%
2.5-4	22-30%
4-10	41%
> 10	69%

PPV = positive predictive value; PSA = prostate-specific antigen.

Table 3: Risk of CaP in relation to low PSA values

PSA level (ng/mL)	Risk of CaP
0-0.5	6.6%
0.6-1	10.1%
1.1-2	17.0%
2.1-3	23.9%
3.1-4	26.9%

PSA = prostate-specific antigen.

Thompson (PCPT 2003)

Overall risk of CaP vs. PSA value

PSA value	<= 4ng/ml	27% chance of malignancy
	4.1-10 ng/ml	41%
	> 10 ng/ml	69%
	> 20 ng/ml	87% (Gerstenbluth 2002)
	20-29 ng/ml	74%
	30-39 ng/ml	90%
	50-99 ng/ml	100%

Threshold value for biopsies not been established. ERSPC data suggest that 7 yr cumulative incidence of cancer is 33% for PSA 3-6, 44% for PSA 6-10 and 71% for PSA >10.
Important to strike a balance between missing clinically significant tumours and overdiagnosing indolent ones. Hopefully long-term data from PCPT may help give an indication of correct level.

Improving specificity (reduced false positives)
Cancer is unlikely when PSA <2.5 and a fair bet when PSA >10.
Grey area in range 2.5 -10 (previously 4-10) which accounts for at least 80% of PSA elevation at presentation. In this group most PSA elevation (~60%) due to benign disease
A number of modifications therefore used to improve specificity of PSA

Free/Total PSA (Catalona 1993)

- Cancers complex – higher risk of cancer when F:T low
- Improves pick-up (Sn) when PSA normal
- Improves specificity when PSA high
- Reduces biopsy rate by 20% whilst maintaining 95% detection rate
- Differing thresholds reported – optimum unknown but < 20% widely used

Recent study of men with PSA < 2.5 showed incidence of 23% CaP, Best predictor was fPSA of ⩽14% - 60% of patients had prostate cancer (Walz 2008)

Table 6.—Probability of Cancer Based on PSA and Percentage of Free PSA Results*

PSA, ng/mL	Probability of Cancer, %	Free PSA, %	Probability of Cancer, %
0-2	~1	. . .†	. . .
2-4	15	. . .	. . .
4-10	25	0-10	56
		10-15	28
		15-20	20
		20-25	16
		>25	8
>10	>50	. . .	. . .

PSA density

In men with normal DRE and PSA 4-10, PSAD > 0.15 ng/ml/ml reportedly a/w increased risk of cancer (Basinet 1994)
May miss up to 50% of cancers ? due to varying amounts of epithelium in equal sized prostates
PSA/TZ density may have higher accuracy (Djavan 1999) but not widely used due to operator dependence issues and low specificity of ~70%

PSA velocity

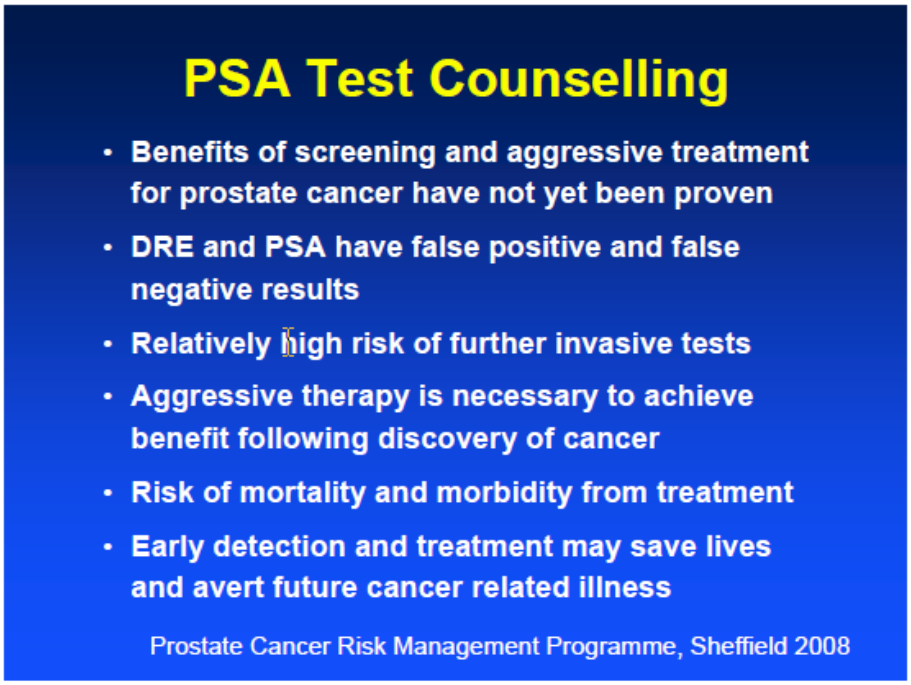
0.75 ng/ml/yr predictive of presence of CaP (Carter 1992*)
Minimum 18 months and three measurements
*Specificity 90% and sensitivity 80% for PSA 4-10. Low sensitivity in patients with PSA <4

Age-specific PSA

Based on 95th percentile in populations of men without CaP
Improves sensitivity in younger men
Improves specificity in older men
Controversial – argued by proponents of radical Rx that may miss too many clinically significant tumours in older men

Table 3. Recommended age-specific PSA reference ranges.

Age range	PSA reference range
40–49	0.0–2.5
50–59	0.0–3.5
60–69	0.0–4.5
70–79	0.0–6.5


PSA Test Counselling
• Benefits of screening and aggressive treatment for prostate cancer have not yet been proven
• DRE and PSA have false positive and false negative results
• Relatively high risk of further invasive tests
• Aggressive therapy is necessary to achieve benefit following discovery of cancer
• Risk of mortality and morbidity from treatment
• Early detection and treatment may save lives and avert future cancer related illness
Prostate Cancer Risk Management Programme, Sheffield 2008

PCA3/DD3 [Progensa PCA3 test; Gen-Probe]
Prostate specific marker identified from differential display (DD3)
Non-translated mRNA, not protein
66-fold increased expression in cancer cf. benign
Present in ~95% of prostate cancers, including mets
Associated with stage and grade. Not associated with prostate volume
Urine test following standardised DRE (3 strokes per lobe) in outpatients
Increased performance vs. PSA at first biopsy: Sp 80% vs. 60% with identical sensitivity (70%), indicating 50% reduction in false positives. Therefore more confidence in positive result (Parekh AUA 2008)
Re-biopsy: Haese 2008 show improved performance vs. PSA. PCA3 > 35 = 39% cancer on second biopsy; (a/w sens. 47% and spec. 72%) which is favourable cf. fPSA of < 25%

TRUS
Cancer hypoechoic on TRUS
Seen in approximately 40% of cancers
But 80% of hypoechoic abnormalities benign
Main role for TRUS in guiding prostate biopsies

Prostate biopsies
Original sextant biopsy using 18G needle described by Hodge et al (Stanford University 1989) – 3 cores on each side in parasagittal plane.
Multiple studies have shown that more initial biopsies improve detection rate
Various techniques reported – no one technique has precedence, but most studies focus on importance of a lateral mid-lobe PZ biopsy. My preferred technique is 'double sextant' (Naughton 2000; modification of Presti)
Even when palpable nodule felt, multiple cores should be obtained due to lower detection rates with fewer biopsies
Routine initial TZ biopsies a/w detection rate of 2% - not recommended
Increased complications reported when biopsies >12 performed.
Reduced detection rate a/w increased prostate volume.
If first set of Bx negative, risk of subsequent cancer diagnosis 10-35%. Study of 1,051 men (European cancer detection study; Djavan 2000)
Biopsy schedule = sextant + TZ x2. All patients PSA 4-10. Negative patients had repeat biopsy after 6 wks.
Detection rates after biopsy #:

#1	22%	
#2	10%	Predictors of cancer low F:T and PSATZ density
#3	5%	
#4	4%	

Cancers detected on first and second biopsy similar (65% organ confined) with equivalent outcomes, indicating biological equivalence. Tumours identified on third and fourth biopsy low grade, stage and volume (? indolent). Similar results in study by Keetch and co-workers. More recently been repeated in patients with extended core biopsy (10 cores) by Mian 2002 [First biopsy 33%; second biopsy 17%; third 0%; 4th 0%]. Only predictor ASAP.

High level (1a) evidence for the efficacy of local anaesthesia from multiple trials – 10ml 2% lignocaine using long spinal needle

Morbidity

Infection	Historical series report asymptomatic bacteriuria in one third and symptomatic infection requiring hospitalisation for IV ABx in 50% prior to prophylaxis. Commonest organism *E coli*, then *enterococcus* Falls to 2% with ABx prophylaxis (best prostate penetration ciprofloxacin, erythromycin, tetracyclines). Poor penetration with co-amoxyclav
Haematuria	Up to 63%; clot retention less than 1%
Rectal bleed	Up to 22%; Apply pressure with probe
Haematospermia	Up to 50%; may last up to 6 weeks
Acute retention	Up to 0.4%

Perineural invasion

No independent prognostic value on pathologic staging
Presence on biopsy a/w increased risk of capsular penetration (~75%) on RRP specimens
Very recent evidence suggesting that perineural invasion a/w increased invasion of large nerves

Staging

Historically 2 classification systems: Whitmore and Jewett and UICC/TNM. Quite similar, but TNM has prevailed.

T - Primary tumour		
	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g., because of elevated prostate-specific antigen (PSA) level)
T2	Tumour confined within the prostate[1]	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule[2]	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall	
N - Regional lymph nodes[3]		
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
M - Distant metastasis[4]		
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*
[2] *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as T3, but as T2.*
[3] *Metastasis no larger than 0.2 cm can be designated pN1mi.*
[4] *When more than one site of metastasis is present, the most advanced category should be used.*

NB. 2002 classification shown above. Effectively re-instated the 1992 classification, dividing T2 into 3 stages, rather than 2 as seen in 1997 classification.

<u>T-staging</u>

Distinction between T2 and T3 has profound impact on Rx decisions
DRE correlates with pathological T-stage in only ~ 50% (Spigelman 1986)
No direct relationship between serum PSA and pathological T-stage
TRUS misses ~ 60% of pT3 tumours
DRE, PSA and biopsy Gleason grade combined in Partin's tables to predict risk of extracapsular extension.
MRI appears to be the most accurate diagnostic modality for indicating ECE

<u>N-staging</u>

Partin's tables may be used to predict risk of nodal mets
Also Gleason grade: Any core with 4+3 or 3 cores 3+4 a/w ~ 30% risk of nodal mets cf. 2.5% risk without.
MRI/CT limited due to poor sensitivity
Operative LND gold standard but obturator fossa not necessarily first site of mets and may cause difficulty with second stage RP

Roach formula
2/3 PSA + (10 x [Gleason – 6]) = % likelihood of LN mets
Originally described in 1988 by Nguyen (J Urol)
Reassessment of value in contemporary series indicates significant overestimation of risk

M-staging
Bony mets in 85% terminal patients – usually sclerotic
Differential diagnosis sclerotic bone mets: prostate, thyroid, lung, breast
Risk of bony mets:

Raised ALP	70%	
Raised ALP & PSA	98%	[Lorente 1996; ? values]
Pre-Rx PSA > 100	100%	[Rana 1992]

ALP but not PSA a/w extent of bony mets, known to correlate with overall survival
Bone scintigraphy (technetium diphosphonates) most sensitive modality for diagnosis of bony metastasis
Multiple studies have shown that Gleason score less than 6 and PSA <20ng/ml risk of bony mets very low and bone scan unnecessary:

PSA < 10 ng/ml	0.5% chance of mets
PSA < 20 ng/ml	2% chance of mets

Nomograms
Partin's tables (Partin 1997; 2001)
Clinical T-stage (DRE) PSA and Bx Gleason score
Based on large number of American pts (n=4133) undergoing RP
Predictive of ECE, SVI, LN mets (although only a limited LND performed in a majority: may therefore underestimate degree of LN mets). Not directly predictive of DFS and mortality
NB. PSA > 10 ng/ml = less than 50% of cancers organ-confined

D'Amico risk stratification: (D'Amico 2001)

Low risk	T2a or less, PSA less than 10, Gleason ≤ 6	10 yr DFS 83%
Int. risk	T2b, PSA 10-20, Gleason 7	10 yr DFS 46%
High risk	≥ T2c, PSA >20, Gleason > 7	10 yr DFS 29%

NICE guidelines very similar, except T2c is in intermediate risk group
Pre-treatment characteristics used to predict the likelihood of DFS after RP
Do not take into account RP findings (final RP grade, ECE, SVI, LNI)

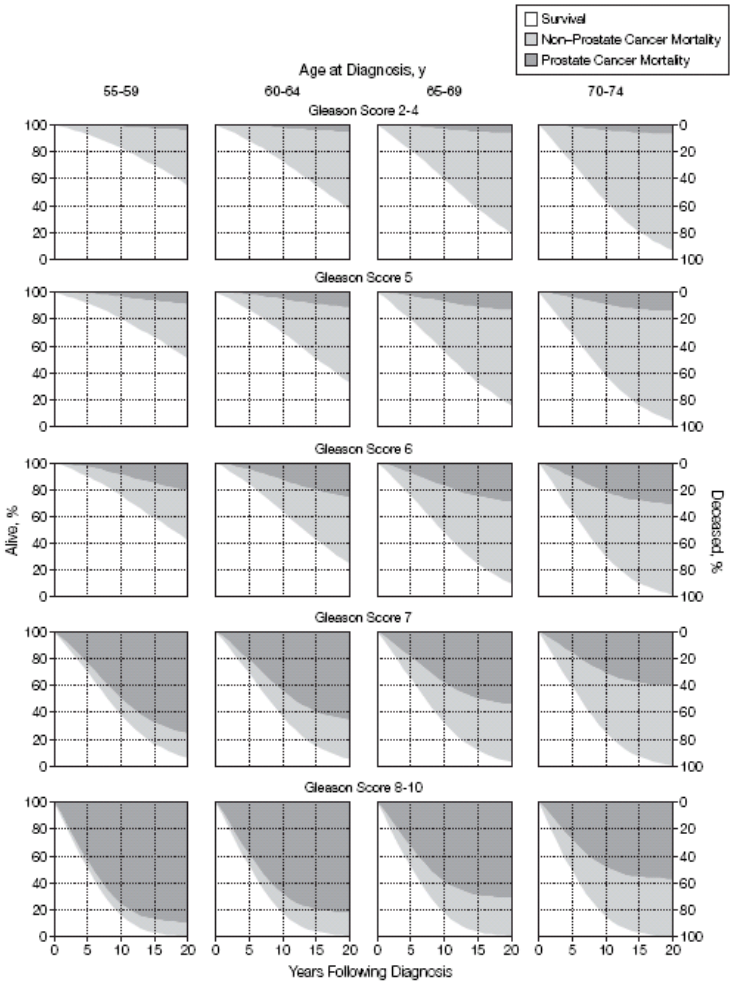
Kattan's nomogram (1998; 2000)
Over 1000 men with clinically localised disease (T1c-T3a) undergoing RP
Pre-Rx PSA, RP specimen grade, surgical margin status - not SVI or LNI
Overall concordance 68%: Recent studies have shown that it may underestimate recurrence in low risk men and overestimate recurrence in high grade disease (Greene 2004). Also now incorporates Kattan's version of Partin's tables. Obtained from MSKCC website.

Natural history of conservatively-managed prostate cancer

Much of the evidence for deferred Rx comes from the pre-PSA era Albertsen study. 20 yr follow-up published in 2006. N=767. Although clinically localised, only 44% of patients had abnormal DRE and only 30% had a staging bone scan. Patients treated with either observation, immediate or delayed hormones. Approx one third of patients had Gleason 2-5 disease. 20 year cancer specific mortality (No difference from 15 yr rates, in contrast to Johansson et al 2004)

Gleason 2-4	7% prostate cancer deaths at 20 yrs follow-up
Gleason 5	14%
Gleason 6	27%
Gleason 7	45%
Gleason 8-10	66%

Even taking account of a high number of Gleason 2-4 tumours, study probably underestimates survival with clinically localised CaP in today's populations with PSA-detected disease. Draisma 2003 has estimated lead-time bias for 55 year old as 12.3 years.



Few studies specifically address the independent effect of stage on outcome in conservatively managed patients. One study (Chodak 1994) reported on T1a patients: 10 yr DSS 96% and 94% for well and moderately differentiated cancers; 10 yr mets-free survival 92% and 78% respectively. Form basis for recommendation of curative intent in patients with T1a Gleason 7 + disease.

Management of localised prostate cancer (pT1-2 N0 M0)

Options: Deferred treatment
Radical prostatectomy
Radical radiotherapy
Cryotherapy/ HIFU

Deferred treatment
Deferred treatment comprises active surveillance and watchful waiting
Active surveillance
- Defer Rx as long as possible to avoid morbidity
- Life expectancy 10-15 yrs
- Regular reassessment of risk
- When Rx instituted – aim is radical cure

Watchful waiting
- Avoid effects of Rx completely in those who may die before requiring it
- Life expectancy < 10 yrs
- Occasional PSA assessment
- Review only when symptomatic
- When Rx instituted – aim is palliation of symptoms

Albertsen data above provide reference by which all outcomes of radical treatment should be compared, particularly given that 44% of patients were T2+ and only 30% had a staging bone scan.
Deferred treatment defined as a treatment strategy which includes a decision to postpone treatment until it is required.
Includes the decision to withhold ADT in older men, but also to delay radical treatment in younger men until signs of disease progression manifest (PSA velocity, upgrading on surveillance biopsy)
Multiple studies have shown that deferred treatment a/w equivalent outcomes to RP and RT in patients with low risk disease. Meta-analysis of six studies (n=828) by Chodak (1994). Results:

	Percentage of patients (95% confidence interval)	
	5 years	10 years
Disease-specific survival		
Grade 1	98 (96-99)	87 (81-91)
Grade 2	97 (93-98)	87 (80-92)
Grade 3	67 (51-79)	34 (19-50)
Metastasis-free survival		
Grade 1	93 (90-95)	81 (75-86)
Grade 2	84 (79-89)	58 (49-66)
Grade 3	51 (36-64)	26 (13-41)

Note **significant metastasis rate in patients with moderately differentiated disease**. Forms basis of recommendation of active surveillance in men with low risk disease. Number of definitions of men suitable for active surveillance:
1. Royal Marsden Criteria
   - Age 50 – 80
   - Fit for radical Rx

PSA < 15ng/ml
Stage T1-2
Gleason 7 or less
< 50% positive cores
Quite risky – very careful follow-up required and probably not transferable to 'real-life' NHS

2. Epstein Criteria
   T1c disease
   Gleason 6 or less
   PSAD < 0.15 ng/ml/ml
   < 3 positive cores
   No core > 50% or > 10mm in length
   Recommended by NICE. More likely to select out 'insignificant disease' only

Klotz et al 2005 (n=299) 85% 8 yr survival in patients with Stage <T3, Gleason 6 (or Gleason 7 in those over 70) and PSA <16 [one third came off surveillance, 15% for PSA progression, 4% for biopsy progression and 3% for clinical progression]. Role of biopsy remains controversial. Klotz advocates Bx at 2, 5 and 10 years. Others believe that Bx unnecessary in the light of stable PSA. PSAV 0.7 ng/ml/yr associated with grade progression on Bx in a recent British study (Ng, Royal Marsden 2009)
Indications for intervention on active surveillance:

PSADT < 2 yrs
Gleason 4 on biopsy
> 50% tissue involved

Radical Prostatectomy
Radical perineal prostatectomy described by Young 1905
Radcal retropublic prostatectomy by Millen 1949
Recommended for patients with a life-expectancy >10 yrs
No comparison with RRT to date. Awaiting results of ProtecT and PIVOT trials (see Prostate Cancer Trials)
Improved disease-specific, overall survival, local progression and metastasis vs. watchful waiting in RCT by Swedish Prostate Cancer Group (SPCG4; Bill-Axelson 2006). n=695. 75% T2 tumours, 84% Gleason 7 or less. At median follow-up of 8.2 years:

Table 3. Cumulative Incidence of the Main End Points and Corresponding Relative Risks.*

End Point	Cumulative Incidence				Absolute Risk Reduction (95% CI)	Relative Risk (95% CI)	P Value
	Radical-Prostatectomy Group		Watchful-Waiting Group				
	total no.	*% (95% CI)*	*total no.*	*% (95% CI)*			
Disease-specific mortality	30		50				
At 5 yr		2.3 (1.2 to 4.6)		4.3 (2.6 to 7.1)	2.0 (–0.6 to 4.7)		
At 10 yr		9.6 (6.5 to 14.2)		14.9 (11.2 to 19.8)	5.3 (–0.3 to 11.0)	0.56 (0.36 to 0.88)	0.01
Distant metastases	50		79				
At 5 yr		8.1 (5.7 to 11.6)		9.8 (7.1 to 13.5)	1.7 (–2.5 to 6.0)		
At 10 yr		15.2 (11.4 to 20.3)		25.4 (20.4 to 31.5)	10.2 (3.1 to 17.2)	0.60 (0.42 to 0.86)	0.004
Local progression	64		149				
At 5 yr		8.1 (5.7 to 11.5)		27.2 (22.8 to 32.3)	19.1 (13.6 to 24.6)		
At 10 yr		19.2 (15.0 to 24.6)		44.3 (38.8 to 50.5)	25.1 (17.6 to 32.6)	0.33 (0.25 to 0.44)	<0.001
Overall mortality	83		106				
At 5 yr		7.8 (5.4 to 11.2)		9.8 (7.1 to 13.5)	2.0 (–2.2 to 6.2)		
At 10 yr		27.0 (21.9 to 33.1)		32.0 (26.9 to 38.2)	5.0 (–2.8 to 13.0)	0.74 (0.56 to 0.99)	0.04

* Analysis of the cumulative incidence was performed with the method of Kalbfleisch and Prentice,[9] and relative risks were calculated with the use of the Cox proportional-hazards model. The absolute risk reduction and relative risk are for radical prostatectomy as compared with watchful waiting. Gray's test was used to determine P values. The mean follow-up period was 8.5 years in the radical-prostatectomy group and 8.8 years in the watchful-waiting group. CI denotes confidence interval.

SPCG 4: *The limitations*

- Non-screen detected cases
- Predominantly T2 tumours, 10% of RP +ve nodes
- Criteria for local progression unreliable
  - DRE, bladder outflow obstruction requiring TURP
- High grade disease excluded
- Pathological stage insufficiently detailed (? positive margins + upstaging ?)
- Morbidity from surgery is high
- Radiotherapy was not evaluated

Recent update (Bill-Axelson 2008) suggests no further improvement in cumulative incidence of death from prostate cancer, distant mets and local progression after 10 years, suggesting that beneficial effect of RP is identified within 10 years of diagnosis with T2 disease. Clearly longer time lag is likely in patients with clinically lower stage disease. Interestingly overall survival became non-significant, although remained better in surgical group.

Table 6: Oncological results of radical prostatectomy in organ-confined disease

Study	No. of patients	Mean follow-up (months)	5-year PSA-free survival (%)	10-year PSA-free survival (%)
Han et al. (2001) (39)	2404*	75	84	74
Catalona & Smith (1994) (40)	925	28	78	65
Hull et al. (2002) (41)	1000	53	–	75
Trapasso et al. (1994) (42)	601	34	69	47
Zincke et al. (1994) (43)	3170	60	70	52

** 15-year, 66%.*

Overall 50-75% cure at 10 years in experienced hands. 10 yr cancer specific survival >95% in majority of studies above.

No effect on PSA recurrence if LND omitted in D'Amico low-risk group. Extended LND recommended in high risk disease but morbidity relatively high (lymphocoele 6.6% vs 2.2% in limited PLND; risk of DVT/PE x10 higher)

Contra-indications to nerve-sparing (likely extracapsular disease)
- cT2c or T3 disease
- Any biopsy Gleason 8 or above
- 2 or more Gleason 7 on ipsilateral side

Complications

From pooled series (EAU):

Complication	Incidence (%)
• Peri-operative death	0.0-2.1
• Major bleeding	1.0-11.5
• Rectal injury	0.0-5.4
• Deep venous thrombosis	0.0-8.3
• Pulmonary embolism	0.8-7.7
• Lymphocele	1.0-3.0
• Urine leak, fistula	0.3-15.4
• Slight stress incontinence	4.0-50.0
• Severe stress incontinence	0.0-15.4
• Impotence	29.0-100.0
• Bladder neck obstruction	0.5-14.6
• Ureteral obstruction	0.0-0.7
• Urethral stricture	2.0-9.0

From BAUS consent form

Mortality	0-1.5%
Infection	5-10%
Bleeding	5-10%
Rectal injury	5%
Impotence	40-60%
Incontinence	50% (5-10% long-term)
BN stricture	5%

Definition of urinary incontinence remains controversial. US studies often defines 'dry' as one pad or less per day. Others believe dry should mean dry

Potency and nerve-sparing procedures

Unilateral NS	~ 50% potent
Bilateral NS	~60% potent

Biochemical disease-free survival after RRP (from Catalona)

Organ-confined	86% 10 yr DFS
T3a -ve margins	65% 10 yr DFS
T3b	25% 10 yr DFS
Microscopic LNI	10% 10 yr DFS

Hormone therapy and radical prostatectomy

Cochrane review (Kumar 2006) NB. EPC trial not included

Neoadjuvant ADT:

- Improved organ-confined rate, down-staging, PSM and LNI
- No improvement in OS or DSS

Adjuvant ADT:

- Improved DSS (OR 3.7)
- No improvement in OS
- EPC Trial (Macleod 2005) – adjuvant bicalutamide 150mg od
  - No improvement in either OS or DSS

Adverse findings after RRP

Factors predicting risk of relapse after RRP:

- Gleason grade
- Pre-op PSA
- Seminal vesicle invasion
- Margin positivity
- Lymph node involvement

Positive margins

'Tumour cells in continuity with inked margin'

RRP associated with positive apical margins

Positive bladder neck margins in RPP

No overall difference RRP vs. RPP

No difference for nerve-sparing vs. non nerve-sparing in matched tumours

No differences for LRP vs. RRP

Overall 30% of pts after RRP have positive surgical margin. Of these ~30% will progress to biochemical failure. Positive apical margins account for ~60%

Adjuvant radiotherapy for adverse pathological findings after RRP

Available evidence from retrospective series suggest 20-83% response rates (clinically undetectable PSA) with salvage RT after RP

Theory and practice suggest RT more efficaceous for low-volume disease

Multiple studies report disease-free survival with low pre-radiation PSA

Forman (1997) – 83% disease-free survival rate with PSA < 2ng/ml compared with 33% if > 2 ng/ml. ASTRO recommends 64+Gy when PSA <1.5ng/ml

Two prospective randomised trials: Bolla 2005 (EORTC 22199) and SWOG (Thompson 2006) have evaluated the role of adjuvant RT after RRP cf. observation:

EORTC = 1005 N0M0 pts with SVI, ECE or LNI randomised to either observation or 60Gy administered over 6 wks (to periprostatic area only, not

wider pelvis). Primary endpoint BDFS. At 5yrs BDFS 72% vs. 52% in favour of RT. Also improved local disease control. No difference in mets-free survival or DSS. Only 23% received salvage radiotherapy.
Thompson = 425 men with T3N0M0 CaP after RRP randomised to 64Gy vs. observation. Longer follow-up of 10.6 yrs. Improved BDFS and local progression. Trend towards improved mets-free survival (p=0.06). No difference in DSS or OS. **Recent 12.5 yr update showed improved OS and metastasis-free survival in early group**. However only 30% of observation group received salvage radiotherapy.

No RCT to date has compared adjuvant RT with early salvage radiotherapy. RADICALS trial currently recruiting. Threshold for salvage RT = two consecutive rises in PSA and PSA >0.1ug/l, or three consecutive rises in PSA. Recent change to eligibility criteria March 2010 in the light of the Thompson SWOG trial clearly showing a survival advantage above. Patients considered to be 'uncertain' re. the benefit of adjuvant radiotherapy now comprise the following:

Gleason 7-10
pT3
Margin +ve
PSA>10

In other words, most men who have a radical prostatectomy are eligible for the RT Timing randomisation.

<u>Radical radiotherapy</u>
Tumour cells heterogenous
Persistence of viable tumour cells after RT (3D-CRT, 75Gy) occurs in up to 50% (Zelefsky 1998)
One study with minimum 23 yrs follow-up after RT showed > two-thirds developed recurrence and half died of prostate cancer (Swanson 2004)
Further data from CaPSURE showed that 92% of 2336 pts required adjuvant HAT for disease progression after 'curative' RT (Grossfield 2002)

<u>External beam RT</u>
Typically beams of photons (gamma radiation); occasionally high-energy protons or neutrons (heavy-particle therapy)
Conventional - opposed rectangular fields including target organ. Damage to 'innocent bystander' organs limits dose
3D conformal - computerised generation on non-rectangular fields to limit injury to other organs. No real-time change in field shape. Allows dose escalation
IMRT - Intensity-modulated. Real-time movement of collimators to adjust dose during treatment. Improves dose escalation whilst limiting toxicity

Low risk	At least 72Gy (a/w 5yr BDFS 69% vs 63% for <72; Kupelian 2005) NICE minimum dose recommendation 74 Gy
Int. risk	78Gy better than 72 Gy (5 yr BDFS 75% vs. 48%; Pollack 2000)
High risk	78 Gy +

Adjuvant hormones after RRT for localised CaP?
Most centres give neoadjuvant or adjuvant hormones on the basis of strong evidence favouring them in locally advanced disease, but very few studies have reported on the efficacy in localised disease. For example in Bolla's EORTC 22863 study, on 8% (34 patients) had high-risk localised disease.
Best evidence to date in localised disease from D'Amico 2004 (n=206). 6 months ADT (CAB with LHRH and flutamide) a/w improved OS and DSS, although numbers very small (6 vs. 0 CaP deaths). Most patients had intermediate disease.
Further study has shown that 6 months better vs. 3 months in localised disease
Current rationale:

Low risk	no hormones
Intermediate risk	6 months
High risk	2-3 years (Gleason score 8+)

NB. EPC data = no evidence of benefit of bicalutamide after RRT for localised disease

Toxicity
30% patients have transient cystitis/proctitis during RT
5-10% have persistent toxicity
50% have erectile dysfunction after EBRT (only 25% after brachyRx)
Increased risk of second malignancies (rectum/bladder): 1.7 fold increased risk of rectal cancer cf. RRP; 2.3 fold risk of developing bladder cancer. (overall 9% chance of second malignancy due to RT – Catto)

Table 9: Incidence of late toxicity by RTOG grade (from EORTC trial 22863)

TOXICITY	Grade 2	Grade 3	Grade 4	Any significant toxicity (≥ grade 2)
	No (%)	No (%)	No (%)	No (%)
Cystitis	**18 (4.7)**	**2 (0.5)**	**0 (0)**	**20 (5.3)**
Haematuria	**18 (4.7)**	**0**	**0**	**18 (4.7)**
Urinary stricture	**18 (4.7)**	**5 (1.3)**	**4 (1)**	**27 (7.1)**
Urinary incontinence	**18 (4.7)**	**2 (0.5)**	**0 (0)**	**20 (5.3)**
Overall GU Toxicity	47 (12.4)	9 (2.3)	4 (1)**	60 (15.9)
Proctitis	**31 (8.2)**	**0**	**0**	**31 (8.2)**
Chronic diarrhoea	**14 (3.7)**	**0**	**0**	**14 (3.7)**
Small bowel obstruction	**1 (0.2)**	**1 (0.2)**	**0**	**2 (0.5)**
Overall GI Toxicity	36 (9.5)	1 (0.2)	0	37 (9.8)
Leg Oedema	**6 (1.5)**	**0**	**0**	**6 (1.5)**
*Overall Toxicity**	*72 (19)*	*10 (2.7)*	*4 (1)*	*86 (22.8)*

LDR Brachytherapy
Low dose rate (LDR) permanent implants.
Iodine-125 or Palladium-103 Half life of iodine is 60 days - decay over 1 yr. Pd-103 decay shorter due to half life of 17 days. Recommended dose 160 Gy and 125 Gy for each. Palladium usually reserved for less well diff. tumours
Indications:
T2a or less, PSA less than 10, Gleason 6 or less
<50% cores positive
Prostate volume <50cc
Flow rate >15 ml/s

Low IPSS score

Contraindications:

Life expectancy < 5 yrs
Coagulation disorder
Previous pelvic irradiation
Gleason 5 disease
Previous TURP
Prostate volume > 50g
Large median lobe
Moderate to severe LUTS (IPSS > 7)
Flow rate < 15 ml/s

Peripheral seed loading as per Paterson and Parker 1943 - reduces urethral damage. Prostate volume increases 20-30% after implantation. Half life of oedema 10 days. Retention rate up to 22%. Worse in glands > 35g, high IPSS, low flow. TURP rate up to 9%. Sx should normalize by 1 yr. Urinary incontinence up to 19% after implants. Much higher if prior TURP - up to 80%. Proctitis rate up to 20%. Usually mild. 70% preserved potency if potent pre-op.

Results:

BDFS 5 yrs = 71 - 93%
10 yrs = 65 – 85%
15 yrs = 53 – 88%*

*Long-term results from Seattle. 88% freedom from PSA failure at 15 years in low risk group (G 6 or less, PSA <10, any T stage). Sylvester 2007

Improved 4 yr BDFS in patients receiving D90 of 140 Gy (92%) vs. those receiving <140 (68%) (Machtems 2006)

No benefit for adjuvant hormones

No evidence for the addition of external radiation to brachytherapy

HDR brachytherapy

Temporary placement of iridium-192 seeds
12-20 Gy in 2-4 fractions followed by 45 Gy
At follow-up of 9 yrs, ~68% BDFS in high-risk group (Galalae 2002)
Signifcant bowel, urinary and erectile problems.

<u>PSA Bounce</u>

Benign PSA rise after EBRT/brachytherapy
Level usually < 1.5 ng/ml
Mean time to PSA bounce ~ 9 months; later after brachytherapy
~30% patients after brachytherapy

<u>Cryosurgical ablation of the prostate (CSAP)</u>

ASA recommended alternative primary radical Rx
12-15 TRUS-guided cryoneedles. Argon gas to freeze, helium gas to warm (Joule-Thompson effect) – protective urethral warmer. Volume <40g to avoid difficulty with pubic arch

Utilises:

Dehydration and protein denaturation
Direct rupture due to ice crystal formation
Vascular stasis and microthrombi leading to ischaemia
Apoptosis

Results

Difficulty interpreting results due to heterogenous definition of treatment failure (PSA 0.5ng/ml commonly used). Irrespective, even the most optimistic studies are inferior to RRP for BDFS in low-risk disease. Early results a/w high complication rate (erectile dysfunction, impotence, retention, urethral sloughing and fistula). Third generation CSAP better but impotence rates remain high (80%)

Long-term efficacy and QOL results not currently available

High-intensity focussed ultrasound (HIFU)

Focussed US waves cause mechanical and thermal (>65C) damage with cavitation, leading to coagulative necrosis

Typically 10g prostate treated/hr – under spinal/GA. Limited to 40g. Rectal cooling to avoid damage

No defined PSA threshold post-op predicting treatment failure, although noted that PSA nadir >1 ng/ml a/w treatment failure in ~ 50%

Urinary retention commonest complication (20%) – BN stricture and subsequent TURP relatively common. BNI often performed at the time of surgery. Urinary incontinence in ~12%. Impotence in ~60%

Progression-free survival reported in 70% at 22 months (Blana 2004).

Long-term efficacy and QOL results not currently available

Management of locally advanced, node-negative prostate cancer (pT3-4 N0/Nx M0)

Options: Radical prostatectomy
Radical radiotherapy
HDR brachytherapy
Hormone ablation

EAU guidelines – consider deferred Rx only in pts with well/moderately differentiated disease and life expectancy of < 10 yrs.

Radical prostatectomy for T3 disease

Surgery for extracapsular disease has traditionally been discouraged
However no randomised trials comparing RRP and RT/hormones in cT3
However ~ 25% of patients with T3 disease on MRI overstaged
No difference in outcome for overstaged and organ-confined cT3 pts.
PSM in up to 66%
LN mets in up to 50%
Adjuvant Rx (RRT/hormones) in up to 75%
Largest study with longest follow-up Ward et al (2005) from Mayo clinic.
n=841. Median follow-up 10.3 yrs.

27% clinically overstaged
78% of T3 patients received adjuvant therapy at a median of 4 yrs following surgery

	10yr	**15yr**
BPFS (PSA>0.4)*	43%	38%
DSS	90%	79%
OS	76%	53%

* progression predicted by Gleason score, PSM, LNI and SVI

Above rates better than RT alone and equivalent to RT/hormones
Current recommendations (EAU)

PSA < 20 ng/mL
cT3a
Gleason 8 or less

Radical radiotherapy for locally advanced disease

Radiotherapy alone is insufficient for treatment of locally advanced disease:

5 yr BDFS < 50%
5 yr OS only 60-70%
10 yr OS < 50%

Additional androgen deprivation therapy has been shown to be effective in the neoadjuvant, concomitant and adjuvant, and adjuvant settings:

Neoadjuvant/concurrent RTOG 86-10 (Pilepich 2001) n= 471 T2-T4 N0M0 prostate:pelvis = 25Gy:45 Gy, 2mo. before and during. At 8 yrs, improved BDFS (PSA<1.5; 24% vs. 10%) and local control. **Improved overall survival in low grade group (Gleason 2-6).**

Concurrent/adjuvant	EORTC 22863 (Bolla 2002) n=415 high grade localised and T3-T4 any grade disease. Mean PSA 30 ng/ml. prostate:pelvis = 20Gy:50Gy. Hormones for 3 yrs. At 5.5 yrs, **improved BDFS, clinical DFS, and overall survival (78% vs. 62%).**
Adjuvant alone	RTOG 85-31 (Pilepich 2001 abstract only). n=977 T3/4 N0/1 pts. More post-RRP T3 and N1 pts in delayed hormones group. prostate:pelvis = 25Gy:45 Gy. Improved 10 yr OS in immediate hormones group (53% vs. 38%)
Neoadjuvant/concurrent/ adjuvant	Laverdiere (1997) n=120 cT2b-T4 Randomised RT alone, 3 mo. of NAD before RT, and 3 mo. of NAD before RT and 6 months of adjuvant AD. Residual cancer on Bx 65%, 28%, and 5% at 24 months. BDFS parallelled biopsy data, indicating value for extended Rx. RTOG 92-02 (Hanks 2003). **Improved BDFS, local control, mets and DFS in patients receiving LTADT** (2mo. goserelin and flutamide before, 2 mo. during and 2 yrs goserelin alone after) vs. STADT (2mo. before, 2 mo. during). No difference in overall survival except in patients with Gleason 8-10 tumours.

Is it just the hormones?
SPCG-7 (Widmark 2009; n=875)
Only trial to report to date, all patients N0
Inclusion criteria (T3 (78%) / T4, N0, M0, PSA <70)
3 months CAB followed by flutamide vs. hormones and addition of RRT (Gy)
At 10yrs, 12% absolute risk reduction in prostate cancer deaths in combined group (11.9% vs. 23.9%) corresponding to 56% relative risk reduction. Also 32% relative risk reduction in overall mortality in combined group. Hormones alone group also three times more likely to have a PSA recurrence than patients receiving additional RT
Minimal increased side-effects in combined group with similar QOL/bother scores (separate publication Fransson 2009)

PR-07	Closed/Awaited
TAP3 trial	Awaited

Management of patients with locally-advanced node-positive prostate cancer (pT3-4 N+ M0)

Radical radiotherapy with prostate boost

Prophylactic pelvic irradiation for patients with intermediate or high-risk disease localised has not been shown to reduce the chances of LN progression (Asbell 1988).

Studies of HAT/RRT in locally advanced disease contained some patients with N1 disease, but too few to assess efficacy. [~4% of patients in Bolla EORTC 22863; not reported in RTOG 86-10]

RTOG 94-13 randomised patients with ~15% chance of LN mets to whole pelvis and prostate RT vs. prostate alone: Progression-free survival improved in patients with combined RT but no difference in DFS or OS

Best data from RTOG 85-31: 95/173 pN1 patients who received pelvic radiotherapy and immediate hormonal therapy had 5- and 9-year progression-free survival (PSA < 1.5 ng/mL) of 54% and 10% cf. 33% and 4% with primary radiation alone and hormonal manipulation at the time of relapse ($p < 0.0001$).

Radical prostatectomy with pelvic LND for nodal metastases

Questionable indication as ~ 100% of patients with clinical N+ disease (on imaging vs. micrometastatic) will relapse.

One retrospective matched study of patients with cN+ disease compared RRP/LND/orchidectomy vs. LND/orchidectomy and found a trend to improved survival which was non-significant (Ghavamian 1999 – Mayo clinic)

No evidence for therapeutic role of LND in clinical N+ disease

Extended LND (20 nodes +) may have a role in pts with limited micrometastasis – no. of nodes correlated with time to progression (Bader/Studer 2002)

Hormone ablation

A number of studies have specifically assessed the role of hormones in non-metastatic, locally advanced disease:

ECOG Messing 1999/2003. HAT vs. observation in 98 men with N+ M0 disease after RRP**. Improved overall survival** 72% vs. 49% favouring immediate HAT (orchidectomy or LHRH analogue monotherapy)

MRC trial 1997. n=938 (501 locally advanced disease). The majority of deaths (67%) were attributed to prostate cancer. Cancer-specific mortality was 55% in the early AD group and 43% in the deferred group (*P* = .001). **Overall survival was also improved in the immediate AD arm (***P* = .02). The reduction in prostate cancer death was primarily due to patients with M0 disease.

EORTC 30846 Schroder. n=302 N+ M0 pts. At median survival of 9.6 yrs **no difference in OS** (trend towards improved survival). 13 year follow-up showed improved OS in immediate group although underpowered.

EORTC 30891 Studer 2006 - randomised 985 patients with non-metastatic PCa (any T, any N) to immediate androgen deprivation with orchidectomy/

LHRH analogues or when evidence of disease required it. Median time to treatment in deferred arm was 7 yrs and 25% pts died before requiring Rx. At median follow-up of 7.3 yrs, no difference in cancer-specific survival, but a **small *reduction* in overall survival in the immediate group**, due to non-prostate cancer deaths. Subgroup analysis showed that in patients with an initial PSA of between 8-50, a PSADT of <12 months identified a group at higher risk of subsequent cancer death. Follow-up schedule was very tight and probably not applicable to UK.

EPC trial Macleod 2005 – At median follow-up of 7.4 yrs bicalutamde 150mg od improved PFS in all patients with locally advanced disease irrespective of standard of care. Objective progression defined as bone scan CT or MRI evidence of progression. OS improved in those undergoing RRT and almost achieved significance in those in the WW group (p=0.06). No difference in RRP group.

Metastastic prostate cancer (M1 disease)

Hormone ablation therapy – Early vs. Deferred
Most historical trials included locally advanced, node negative, locally advanced node positive and M1 patients. Trials which include M1 patients comprise VACURG and MRC trials.

VACURG I (Veterans Administration Cooperative Urological Research Group) (Jordan 1977). Stage 3/4 patients randomised to 5mg DES, orchidectomy alone, both or placebo. Improved progression-free and DSS with all 3 HAT arms but increased deaths due to cardiovascular complications.

VACURG II (Byar 1973) n=1506 men with stage III/IV disease to placebo or one of three doses of DES (0.2 mg, 1 mg, 5 mg). DES at 1 mg and 5 mg delayed progression of stage III disease, and **patients receiving 1 mg had improved overall survival and no increased cardiovascular toxicity**. 5mg dose again resulted in increased cardiovascular death. Subsequent analysis suggested that immediate estrogen therapy was most beneficial in patients younger than 75 years with high-grade tumors (Gleason sum 7 to 10).

MRC trial (1997) n=938 (501 non-metastatic; 261 confirmed mets; 173 unknown). No evidence of overall survival benefit in in those with confirmed/unknown disease. However **pathological fracture, spinal cord compression, ureteric obstruction and channel TURP all significantly reduced in early hormones group.** Study has been criticised because those in the deferred arm received salvage therapy very late, but differences very robust.

Cochrane review of pooled patients (n=2167) from 4 trials [ECOG; MRC 1997; VACURG-I; VACURG-II] showed improved progression-free survival and small increased benefit in overall survival (OR 1.16 at 10 years) for patients receiving immediate vs. deferred treatment. The percent overall survival at 1, 5, and 10 years was 88% vs. 86%, 44% vs. 37%, and 18% vs. 12%. for early treatment group vs. deferred group respectively.

Arguments for early hormones:
- More effective early in disease
- Evidence that it improves overall survival in locally advanced non-metastatic disease (MRC 1997, Messing 1999; Macleod EPC significant at p=0.06 level; Studer PSA > 8 and PSADT < 12 mo.)
- Prevents complications

Arguments against early hormones:
- No evidence of overall benefit in patients with metastatic disease (except in VACURG II)
- Reduced cost
- Reduced complications due to hormone ablation
  - Hot flushes
  - Loss of libido
  - Erectile dysfunction
  - Other

Weight gain, hair loss, gynaecomastia, testicular and muscular atrophy
Mood change, depression, anxiety, cognitive decline
Osteoporosis, anaemia, hyperlipidaemia, abnormal LFTs
Diarrhoea, cholelithiasis
CVA, MI, DVT *
Decreased light accomodation, alcohol intolerance, interstitial pneumonitis **

* DES and CPA
** nilutamide

Antiandrogen monotherapy

Bicalutamide 150mg monotherapy inferior to castration in patients with metastatic disease, although difference in median survival only six weeks. No difference in survival in M0 disease (Iversen 2000)

Complete androgen blockade (CAB)

Castration reduces circulating by 95%
Peripheral conversion of adrenal androgens into DHT by 5-AR continues
Multiple studies comparing CAB vs. monotherapy. Results contradictory
- Prostate Cancer Trialists Lancet 2000, showed 2% survival advantage for CAB but not statistically significant at 5 years
- Cochrane systematic review 2000, 20 trials over 6000 patients - %5 improvement in DSS not OS at 5 years

Most benefit in patients with LHRH analogues and non-steroidal anti-androgen
Benefit only seen after combination therapy for 5 yrs
Increased side effect profile
Estimated cost per QALY $1 million US vs. orchidectomy

Intermittent androgen deprivation therapy (IADT)

Castrate-resistant disease arises on average after 24 months of continuous therapy - reasons unknown. Intermittent ADT may theoretically prevent the selection of AI clones whilst simultaneously improving QOL and reducing cost
Currently no evidence that IADT improves either DSS or OS. **However emerging evidence of equivalence c.f. continuous ADT**

- De Silva 2009
  - Southern European Study Group (n=626)
  - PSA threshold 20ng/ml if no Sx or 10ng/ml if Sx (assuming PSA fell to below 4ng/ml)
  - No difference in CSS or OS
  - More cancer deaths in IADT group but more cardiac deaths in CADT group (non-significant)
  - Reduced side-effects and better sexual performance in IADT
- Hussain 2006
  - SWOG 9346; closed and ongoing
  - Early abstract suggested equivalency but results immature

UK study (Lane 2004) gave IADT to patients achieving PSA < 4 or >90% fall after 9 months of ADT. 9 month cycle re-instituted when PSA > 20. 86% of men alive at median follow-up of 134 mo.

Peripheral androgen blockade

Relatively new concept
Combination of 5-ARI and non-steroidal antiandrogen
Maintains serum tetosterone and sexual function
Early results suggest substantial PSA reponses (96%)
Largest study has reported prolonged castration-free and hormone-responsive disease rates of up to 4 years (Oh WK, 2003) – sexual function preserved in >50%

Emergent management of spinal cord compression

Hormone-naiive patients – Ketoconozole (Nizoral) 400mg po q. 8 hours +/- dexamethasome 8mg bd until radiotherapy. Alternatively immediate orchidectomy. Give PPI cover. Tail down steroids by half every three days after radiotherapy. Aim to give LHRH analogue after one week and stop ketoconazole after three weeks. If LFTs abnormal consider changing to CPA or bicalutamide.
Hormone-refractory patients – Urgent steroids and RT. Could also try antiandrogens/ketoconazole but response usually less dramatic as for hormone-naiive patients

Follow-up after treatment with curative intent

Defining progression after curative treatment

Expect for rare cases of undifferentiated tumours **all** patients developing clinical relapse have a preceeding PSA rise (Pound 1997). May therefore be used for surveillance after treatment.

Relapse may be local or systemic. Data from Stephenson et al below

Factors predicting local relapse:

- Time to PSA rise > 2 years
- PSADT >= 11 months
- Gleason score <= 6
- Pathological stage <= T3a (+/- margin positivity)

Factors predicting systemic relapse:

- Time to PSA rise > 2 years
- PSADT 4-6 months
- Gleason score >= 7
- Seminal vesicle invasion
- Lymph node invasion

Parameter	Local recurrence	Systemic recurrence
Interval to PSA relapse		
≤ 1 year	7%	93%
1–2 years	10%	90%
> 2 years	61%	39%
> 3 years	74%	26%
PSA doubling time	11.7 months	4.3 months
Gleason Score		
2–4	0%	0%
5–6	55%	45%
7	39%	61%
8–10	11%	89%
Pathological stage		
Organ confined (≤ pT2b)	40%	60%
pT3a, R0	54%	46%
pT3a, R1	48%	52%
pT3b	16%	84%
pTxpN1	7%	93%

After Radical Prostatectomy

Definition:

- Amling 2001 followed 2,782 men after RRP
  - PSA 0.2 – 49% chance of further PSA rises
  - PSA 0.4 – 72% chance of further PSA rises
- Therefore current consensus:
  - **2 consecutive PSA values >= 0.2 ng/ml**

Evaluation of PSA relapse:

- DRE unhelpful in 95% of cases (Obek 1999)
- TRUS/Bx – positive confirmation in only 50% (except hypoechoic - 80%). Generally unhelpful – rely on PSA.
- Bone scan and CT/MRI scans unhelpful unless PSA > 20ng/ml or PSA velocity > 20ng/ml/yr
- Endorectal MRI reportedly accurate in ~80% (Sella 2004)

Radiolabelled (11C) choline PET scanning and immunoscintigraphy (111-indium capromab penetide – monoclonal antibody for PSMA) promising, especially when PSA > 1ng/ml, but not widely used.

Treatment:

Options

Observation
Salvage radiotherapy
Hormone therapy

(i) Observation

Potentially an option in those unfit or unwilling
For pts with local recurrence with Gleason <=7 disease, time to mets ~ 8yrs and time from treatment of mets to death further 5 yrs

(ii) Salvage radiotherapy

Local recurrences only
More effective when PSA low (Forman 1997; Nudell 1999)
ASTRO recommend at least 64 Gy when PSA < 1.5 ng/ml (Cox 1999). Some authors believe that threshold too high.
5 yr DSS and OS = 69% and 96% for impalpable disease (Macdonald 2004)

(iii) Hormone therapy

Systemic and high-risk local recurrences
Evidence of **reduced risk of clinical progression in pts receiving early ADT** vs delayed. No survival benefit however (Moul 2004)
Some evidence of survival advantage in men with N+ disease after RRP (Messing). Possibly additional benefit in men with high risk disease (Pre-Rx PSA >20, Gleason 8+, SVI, LNI)
Antiandrogens suitable alternative to castration in locally advanced disease (no survival benefit but decreased prog.)
Trials of intermittent ADT and fin/flut small with short follow-up

<u>After Radical Radiotherapy</u>

Definition:

Astro (Phoenix) **PSA increase >= 2ng/ml above nadir**
Previous ASTRO criteria 3 consecutive PSA rises with time of relapse backdated to half-way between nadir and rise one.

Evaluation of PSA relapse:

As for PSA relapse post-RRP
Prostate biopsy only indicated if salvage therapy considered appropriate. Should be performed at least 18 months after Rx (ASTRO)

Treatment:

Options:

Salvage prostatectomy
Cryotherapy
HIFU
Hormones

(i) Salvage prostatectomy

Historically associated with significant complication rates, including severe incontinence and rectal injury
One of largest series from MSKCC (Stephenson 2004; n=100) reported relatively low complication rates: impotence 72%, severe incontinence (32% - 23 pts had AUS), rectal injury 2%
Similar progression-free survival cf. primary RRP
10 yr DSS 70-80%
10 yr OS 60-70%
Improved prognosis in organ-confined disease, No LNI, SVI or positive surgical margins and low pre-treatment PSA
Generally recommended for those with:

- Good performance status
- Life-expectancy > 10 yrs
- Gleason < 7
- Relapse PSA < 10 ng/ml
- Organ-confined disease

(ii) Cryotherapy

Poor efficacy and high complication rates likely to limit application
Pfisters 1997 n=110 after RT – 70% biochemical relapse post-treatment. High rates of incontinence (~30% at 1 yr), impotence, perineal pain (up to 40%) and urinary fistula.
Similar high rates of complication

(iii) Salvage brachytherapy

As for salvage CSAP

(iv) HIFU

Small numbers and minimal follow-up.
Initial experience not great. Gelet 2004 – PSA progression in 56%, BN stenosis in 17% and fistula in 6%
Should be regarded as experimental.

(v) Hormones

Early vs. delayed hormones debate
One study specifically in men with PSA relapse after RRT found 5 yr DSS and OS rates of 92% and 76% respectively.
Immediate hormones improved metastasis rates in those with a PSADT < 12 months. No difference in those with PSADT > 12 months. (Pinover 2003. Fox Chase Cancer Centre, Philadelphia)

Castrate resistant prostate cancer (CRPC)

Mechanisms of androgen independence

Current theories regarding mechanisms of androgen-independence (AI) have centred on the pivotal role of the androgen receptor:

(i) AR amplification - 20-30% of hormone-independent tumours
(ii) AR mutations – typically at hotspot in exon 5 Xq11-12 (AR gene)
gain-of function
hypersensitivity
promiscuity (i.e. androgen withdrawal effect)
(iii) Ligand-independent activation/modulation
IGF-1, EGFR cAMP
General steroid receptor co-regulators
Specific AR co-activators (supervillin family)
Oestrogens
(iv) Non AR-dependent pathways (p53 mutation, c-myc and bcl-2 overexpression)

Clinical features

Truly castrate resistant prostate cancer should be differentiated from androgen ablation insensitive disease (AAID) by the following criteria:

1. Castrate levels of serum testosterone (T< 50ng/ml or 1.7 nmol/l)
2. 3 consecutive PSA rises >= 1 week apart resulting in 2 50% increases over nadir
3. Antiandrogen withdrawal for at least 4 weeks (or failure of second line hormonal manipulation)
4. Progression of osseus or soft-tissue metastasis

NB. Castration levels = early morning serum testosterone <20-50 ng/ml

Overall survival in true HRPC:

Patient characteristics	Estimated mean survival
Asymptomatic PSA ↑	
• No metastases	24 - 27 months
• Minimal metastases	16 - 18 months
• Extensive metastases	9 – 12 months
Symptomatic PSA ↑	
• Minimal metastases	14 - 16 months
• Extensive metastases	9 - 12 months

PSA and HRPC

A PSA response >= 50% associated with significant survival advantage (Kelly WK, (MSKCC) 1993; 8.6 months vs. 25 months) particularly if response maintained for at least 8 weeks (Smith DC 1998; 91 weeks cf. 38 weeks)

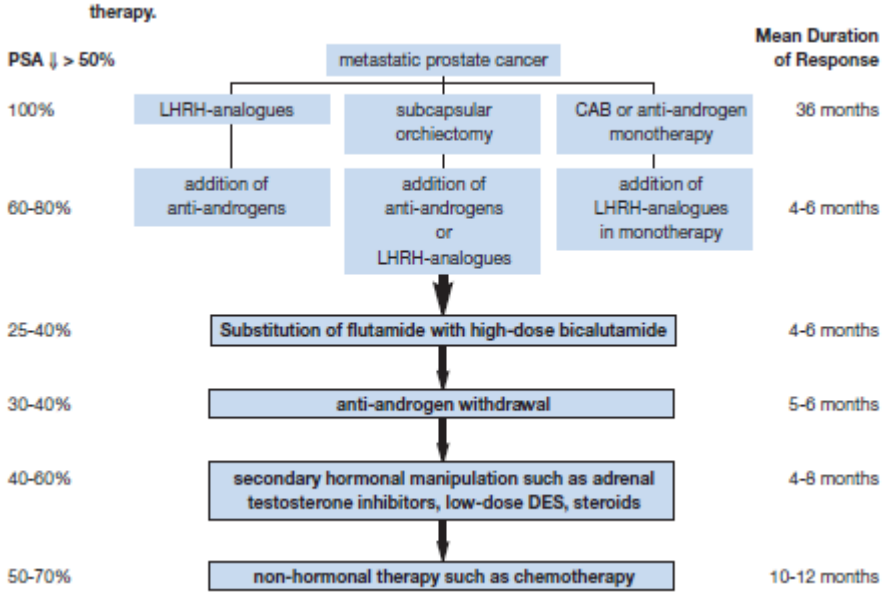
Does androgen ablation therapy need to continue in the face of AAID?

Probably but little evidence. Manni 1998 evaluated 85 patients with AAID after orchidectomy. All received complete androgen blockade and chemotherapy. Randomised to androgen boost or no boost. Those receiving androgen boost did worse (median survival 10 vs 15 months). Two other studies have also

shown a modest survival advantage (Taylor 1993; Hussain 1994). However good theoretical reasons for continuing androgen ablation as above.

Management options

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy.



Secondary hormonal manipulation

A number of studies have identified prolonged PSA responses in patients receiving second-line therapy for AAID. Options include antiandrogens (high dose bicalutamide/flutamide), adrenal androgen suppressants. (aminoglutethimide, ketoconozole, steroids), or oestrogens. Recent evidence from Suzuki 2008 showed >60% response for changing antiandrogen after a period of antiandrogen withdrawal. Moreover responders had significantly better survival Absence of good quality randomised data. No randomised study to date comparing sequential therapy vs. 'standard therapy' (e.g. NICE recommended). Thus **second-line hormonal therapy recommended for asymptomatic AAID patients with PSADT > 6 months.**

New agents - Abiraterone acetate

Patients with hormone-relapsed prostate cancer still display AR-positivity. Most theories of androgen deprivation insensitivity centre on resetting of AR pathway threshold (ie AR amplification, hypersensitivity mutation, promiscuity etc.). Recent therapies have centred on inhibiting androgen production rather than targeting the androgen receptor. **Attard 2008** reported phase I results of **abiraterone acetate** on 21 chemotherapy-naïve men with HRPC. Abiraterone acetate is a small molecule inhibitor of cytochrome CYP17, the enzyme responsible for 17-alpha hydroxylation (see below). PSA responses greater than 30% were seen in two-thirds (duration not reported in abstract, tumour volume responses in ?80%). Side effects were related to mineralocorticoid excess (high BP, oedema, hypokalaemia) requiring receptor antagonist therapy. Further phase two and three trials awaited to determine if any improvement in disease specific survival. NB. Prolonged therapy may have

significant deleterious effect on BMD, as levels of oestrogen and androgen are reduced with CYP17 antagonism.

Chemotherapy

Traditionally response of PCa to chemotherapeutic agents poor. US CALBG 9182 and further Canadian study demonstrated benefit of mitoxantrone and prednisolone for improvement in PFS, pain and QOL, but no improvement in overall survival. TAX 327 and RTOG 9906 recently demonstrated small overall survival benefit of docetaxel and prednisolone in metastatic PCa.

TAX 327 Tannock 2004 (n=1006, median age 68)

q3wkly docetaxel 75mg/m2 vs. weekly docetaxel vs. mitoxantrone and prednisolone. All patients also received 5mg bd prednisolone.
q3wkly group showed **2.4 mo increased overall survival** cf. mitoxantrone (18.9 vs. 16.5) at 15 months. Benefit in all age groups.
Improved secondary endpoints (PSA response, pain, QoL)
Only **one third of patients responded**
Significant increased side effects in docetaxel group - one third grade 3/4 neutropenia, lethargy
Docetaxel expensive - £27,000 for 19 months treatment, as only one third of patients respond, therefore conservative estimate of cost of improveing one patient's life by 2 months is ~ £80,000.

SWOG 99-16 Petrylak 2004(n=674)

Compared docetaxel and estramustine with mitoxantrone and prednisolone. Overall survival in docetaxel arm 1.9 months better but side effects worse due to estramustine.

Recent studies combining taxanes with thalidomide (Dahut 2004) have shown improve responses but significant rates of thromboembolic complications (28% vs 0%) in combination arm. Ongoing combination studies continue.

Progression after taxane chemotherapy

All patients will progress after taxane based chemotherapy
SPARC trial (n=950 ongoing Sternberg)) showed a 40% response rate for satraplatin and prednisolone vs. prednisolone alone for second line chemotherapy. However final results published in 2009 – no improvement in overall survival. Promising results for:
Cabazitaxel (TROPIC trial – abstract only 2010)

All patients progressing on docetaxel chemoRx
30% reduction in risk of death
Absolute increase in survival of 2.4 monthgs cf. mitoxantrone and pred

Provenge (sipuleucel-T)

Dendritic prostate cancer vaccine
Improved 3 yr survival by 40% in those with CRPC

Management of bone complications

Strontium-89, Samarium-153 and bisphosphonates all shown to reduce bone pain by ~70%

However Strontium-89 and Samarium-153 a/w myelosuppression which may prevent subsequent chemotherapy
No evidence for IV pamidronate or oral clodronate in metastatic prostate cancer with bony mets. Zoledronic acid third generation bisphosphonate shown to reduce skeletal related events in HRPC with bone mets. Landmark paper Saad F 2002 (n=643). 4mg **zoledronic acid in** 100ml infusion every three weeks for 15 months **associated with 11% reduction in skeletal related events (**fracture, SCC, bone surgery, bone radiation, bone pain: however only pathological # rate significantly different among groups; most of the changes due to bone radiation) **at 15 months compared with placebo** [44% vs. 33%]**.** Only 30% of patients completed treatment. Very expensive - £195 per treatment. NNT - 9 patients to prevent one skeletal related event = £38,000. Fever, myalgia, hypocalcaemia and elevated creatinine worse in zoledronic acid group (0-5% difference cf. placebo)

Palliative RT for symptomatic bone mets = 30Gy in 10 fractions

Differential diagnosis bone metastases

<u>Lytic bone mets</u>
Renal
Thyroid
Hepatocellular
Breast
Lung
Colon

<u>Sclerotic bone mets</u>
Prostate
Breast
Colon
Melanoma
Bladder
Sarcoma

Improving population outcomes in prostate cancer

Population screening

Definition

Testing for disease in a population of asymptomatic individuals with the intention of modifying the natural history of that disease

Types of screening

Opportunistic
Targeted or selective
Mass screening (defined by Wilson and Junger)

Wilson and Junger criteria (10)

Important health problem
Natural history should be understood
Recognisable latent or early phase
There needs to be a suitable test to examine for the disease
Screening test must be acceptable to the population
Treatment must be acceptable
Agreed policy on whom to treat as patients
Facilities for diagnosis and treatment available
Screening must be repeated according to natural history
Cost should be economically balanced

<u>Evidence supporting screening for prostate cancer</u>

<u>Epidemiological data</u>

Following introduction of PSA testing in early 1990s, incidence of prostate cancer in US increased dramatically, then decreased *along with mortality*. Often cited as evidence for beneficial role of screening in prostate cancer.. However a study from 2 areas of US with differing rates of PSA testing showed no difference in prostate cancer mortality (Lu-Yao 2002), although patients in this study elderly and may not have benefited. However similar response seen in UK, with much lower rates of opportunistic/targeted PSA testing. Epidemiological evidence for screening comes from Tyrol longitutudinal cohort study (Bartsch 2001), which showed 44% drop in observed vs. expected prostate cancer deaths in Tyrol compared with rest of Austria.

<u>Randomised controlled trials</u> (3)

Important to appreciate that randomisation should eliminate any lead-time bias. Ideally can only definitively conclude a definite effect when more than 50% of patients in each arm have died.

Quebec study (Labrie1999)

n=46,193 men randomised to either screening or observation
PSA threshold 3ng/ml
Major problems with compliance – only ~20% of men randomised to screening were screened.

Originally 69% reduction in CaP mortality reported – **non-significant on intention-to-treat analysis**

ERSPC (Schroder 2009)

n=182,000 (162,243 between 55-69)
Multicentre trial
PSA threshold most commonly 3ng/ml
3.8% CaP deaths in screening arm vs. 7.6% in observation arm at median follow up of 9 years
PSA screening reduced cancer-specific death rates by 20%
No difference in overall survival
NNT very high – 1410 men screened and 48 cases of prostate cancer treated to prevent one death.
[NB. Breast cancer screening requires ~ 1000 women to be screened but only 6 treated to prevent one death]
Large differences in rates of metastasis likely to widen gap and reduce NNT in future analyses: recent study from Hugosson Lancet 2010 from Goteburg has reported long-term outcomes in Scandinavian subpopulation incorporated into ERSPC. 293 screened, 12 treated to prevent one CaP death. Attempts underway to stratify those most likely to benfit from routine screening. Vickers et al Lancet 2010 have show that at PSA 1.0 or less at 60 yrs old a/w with a very low risk of prostate cancer death

PLCO (Andriole 2009)

n= 76,693
US trial
Heavily contaminated – 52% of patients in the control arm screened!
Results therefore highly dubious and likely to be underpowered when analysed by intention to treat
At median follow-up of 10 years, no difference in either DSS or OS

Chemoprevention

PCPT (Thompson NEJM 2003)

n=18,882, median follow-up 7 years
>= 55 yrs, PSA <= 3 and normal DRE
Patients randomised to **finasteride 5mg od** vs. placebo
Annual DRE and PSA. If PSA >= 3 (Doubled in finasteride group) or if abnormal DRE, referred for biopsy.
Steering committee worried that finasteride may induce confounding (altered texture making abnormal DRE more common etc.) Therefore incorporated end-of-study biopsies.
End of study biopsies - markedly increased observed CaP prevalence from that predicted by SEER data (6% - Cooner 1990)
Overall prevalence 24.4% in control group compared with 18.4% in finasteride = **24.8% reduction in prostate cancer incidence**.
Reduction consistent irrespective of age, race, family history and initial PSA
Significant prevalence in pts with low PSA (data from control arm)

Sexual side effects (reduced ejaculate volume, impotence, loss of libido and gynaecomastia) more common and LUTS less common in finasteride group
Prostate volume 24% lower in finasteride group cf.controls
Higher proportion of Gleason 7+ in finasteride group (6.4%) cf. controls (5.1%). Theories:

1. Induction by finasteride – but no yr-on-yr increase seen. Some theoretical sense. Type 2 5-ARI reduced in increasing Gleason grade and ligand activation of ER-beta results from breakdown of DHT
2. Histo altered by finasteride – no evidence for this as yet
3. More likely to pick up HG cancers in smaller glands – this also assumes that HG disease less responsive to 5-ARI than low grade disease

REDUCE (Andriole NEJM 2010)

'REduction by DUtasteride of prostate Cancer Events'
Dutasteride inhibits type 1 and type 2 5-ARI (type 2 most common iso-enzyme in prostate – selectively inhibited by finasteride)
Expression of type 2 5-ARI reduced with increasing gleason grade cf. type 1, which increases with gleason grade.
Double inhibition a/w more significant reduction in DHT in both prostate and serum.
n = 6729
Median follow-up 4 years
Inclusion criteria (different from PCPT – higher risk patients)

- 50 – 75 years
- Negative biopsy x1 in 6 months prior to enrolment
- PSA 2.5 -10
- Scheduled 10 core biopsies at 2 and 4 years

Results

- Dutasteride a/w reduction in prostate cancer incidence:
  - Absolute reduction of 5.2% (19.1% vs. 25.1% for placebo)
  - **Relative risk reduction of 22.8%**
- Slightly higher incidence of high-grade tumours in dutasteride group but non-significant
- Well tolerated – 5% loss/reduction in libido; 9% erectile dysfunction. Statistically higher incidence of cardiac side effects

SELECT (Lippman 2009 JAMA)

Selenium and Vitamin E cancer Prevention Trial
n = 35,533
>= 55 yrs, PSA <4 and normal DRE
PC-randomisation to selenium (200 ug/day) vitamin E (400IU/day) or both to determine if any advantage in reducing prostate cancer risk
Trial stopped at median follow-up of 5.5 yrs due to lack of effect

PHS II (Gaziano 2009 JAMA)

Physicians health study #2

No chemopreventive effect for either vitamin E (400IU alternate days) or vitamin C (500mg/day)

Appendix

Pharmacology - Hormone ablation therapy

(i) Oestrogens

- Mechanism of action
  - Downregulation of LHRH secretion (negative feedback)
  - Antagonism of androgens
  - Direct suppression of Leydig cell function
  - Direct prostate cancer cell cytotoxicity
- Efficacy comparable with bilateral orchidectomy (Seidenfeld 2000)
- Also effective in HRPC – up to 86% response rates
- Theoretcal benefits a/w oestrogen receptor beta activation
- Side effects
  - Cardiovascular toxicity (3mg and 5mg doses – no anticoagulant)
    - Due to first pass hepatic metabolism producing thrombogenenic metabolites
  - Cardiovascular mortality avoided by by parenteral administration (polyoestradiol phosphate - SPCG-5, Hedlund 2002; although overall non-fatal cardiovascular adverse events higher), or administration of anticoagulants (Klotz 1999)

(ii) LHRH agonists

- Mechanism of action – desensitisation of androgen receptors.
- a/w flare –occurs 2/3 days after injection and lasts one week.
- Recommended that antiandrogen started with injection and continued for 2 weeks. **May not be prevented with antiandrogen Rx**
- As flare can have catastrophic outcomes in men with high volume metastatic disease, other forms of dramatic T suppression (orchidectomy/ketoconozole) should be considered in men with incipient spinal cord compression.
- Castrate levels of testosterone after 2-4 weeks
- 10% fail to achieve castrate leveles with LHRH agonists

(iii) LHRH antagonists

- Immediate, rapid LH and FSH suppression without flare
- Serious problems with life-threatening histamine reactions 1-3% pts
- Recently Abarelix reported to be as effective as leuprorelin and CAB without any increased SE
- However, Degarelix associated with chills in 4% and pain at injection site in ~40%

(iv) Antiandrogens

- Compete with T for binding sites on AR
- Steroidal (CPA, megestrol, medroxyprogesterone) and non-steroidal (nilutamide, flutamide and bicalutamide)
- Non-steroidal pure blockers of AR; Steroidal also inhibit pituitary via negative feedback. **Therefore serum testosterone normal/higher with bicalutamide, lower with CPA.** Non-steroidal antiandrogens therefore a/w retained libido, erections and bone mineral density

a) Cyproterone acetate (S)
- Significantly poorer OS vs. LHRH analogues (Moffat 1990) when used as monotherapy
- No dose-finding study ever performed.
- 100mg tds recommended – half life 30-40 hours
- SE Cardiovascular toxicity (4-40% EAU)
  - Hepatotoxicity

b) Medroxyprogesterone acetate (S)
- Significantly poorer OS when compared with CPA or DES (EORTC 30761, Thorpe 1996) – historical for Rx
- 20 mg od very effective for Rx hot sweats

c) Nilutamide (NS)
- Dose 100mg tds
- No comparative trials of monotherapy vs. castration
- a/w significant side effects > bicalutamide
  - Delayed adaption to darkness
  - Alcohol intolerance
  - Hepatotoxicity
  - Interstitial pneumonitis
- May have a role in HRPC (Kassouf 2003)

d) Flutamide (NS)
- Dose 750mg tds – half life 5-6 hours
- Commonly used in US, probably as early phase II studies showed **preservation in sexual function in 80%**. (Longer term studies however showed preservation in only 20% at 7 years – EORTC 30892, Schroder 2004)
- Equivalence to orchidectomy and CAB for OS (Boccon-Gibod 1997)
- SE diarrhoea
  - hepatotoxicity

e) Bicalutamide (NS)
- 50mg dose ineffective vs castration – no difference for 150mg dosage in terms of PSA response. 50mg dose reserved for second-line hormonal Rx.
- Bicalutamide assessed in a number of settings:
  - Localised disease (EPC)
    - **No evidence for adjuvant bicalutamide in addition to standard therapy in localised disease**
    - Detrimental effect on OS in WW
  - Locally advanced disease
    - Improved PFS with adjuvant bicalutamide when given in addition to standard therapy in locally advanced disease (EPC)
    - **Improved OS when given adjuvant to RRT** (EPC)
    - **Equivalent to castration in M0 disease** (Iversen)
  - M1 disease
    - **Inferior to castration in M1 disease** (Iversen)

SE Breast pain*
Gynaecomastia*
Hot flushes

* Peripheral conversion of T to E a/w gynaecomastia and breast pain
* may be ameliorated by radiation to breast buds - ? reference